EXHIBIT 1, Tab 2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20905

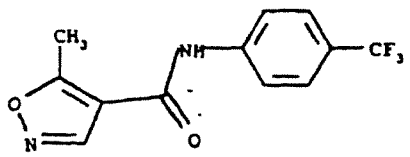
CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

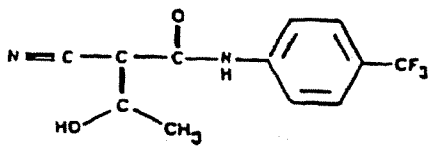
NDA:	20-905 (ORIG)	SUBMISSION DATE: 3/11/98, 4/20/98 4/24/98, 5/15/98, 5/28/98/, 6/3/98 6/15/98,6/23/98,6/24/98
PRODUCT:	ARAVA™ Leflunomide Tablets	
SPONSOR:	Hoechst Marion Roussel Kansas City, MO 64137	REVIEWER: Veneeta Tandon, Ph.D.

I. Background

Leflunomide is a pyrimidine synthesis inhibitor with antipoliferative effects intended for use in the treatment of rheumatoid arthritis (RA). Chemically, leflunomide is an isoxazole derivative with the chemical name N-(4'-trifluromethylphenyl)-5-methlisoxazol-4-carboxamide. The compound was originally developed as an anti-inflammatory agent, but due to significant immunomodulatory activity, development of the compound was directed towards the treatment of autoimmune diseases.



Leflunomide



A77 1726 (major active metabolite)

Following oral administration leflunomide is rapidly metabolized to A77 1726, which is presumed to be the active drug product. The active compound A77 1726, is the ring open metabolite of leflunomide with a chemical name 3-cyano-3-hydoxy-N-)4-trifluoromethyl-phenyl)-crotonamide.

Dosage and Administration: It is recommended that therapy be initiated with a 300 mg loading dose administered as a single 100 mg dose per day for 3 days, followed by daily maintenance dose of 20 mg. In the event of tolerability issues, the dose may be decreased to 10 mg daily.

II. Recommendation

From a biopharmaceutics standpoint of view the sponsor has adequately described the pharmacokinetics of ARAVA, based upon the plasma concentrations of the major active metabolite (A77 1726) of leflunomide in healthy subjects and patients with RA. The parent drug leflunomide was occasionally seen at very low levels. The sponsor at the

very end stages of the review requested that the use of 5 x 20 mg tablets be allowed as an alternative to the 1 x 100 mg as the loading regimen for leflunomide. This will not be an approvability issue for this application and will be addressed separately. Considering the size of the review, the labeling for leflunomide will also be dealt separately. Currently, the application is approvable from the pharmacokinetics standpoint, contingent upon addressing the issues regarding polymorphs and dissolution specifications (see comments 1 and 2 on page 52).

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III. Formulation

The formulation for the 10 mg, 20 mg and 100 mg tablets is shown in the table below. 10 and 20 mg are proportionally similar, except for the change in the active ingredient, other ingredients remaining the same.

Ingredient
Leflunomide
Lactose Monohydrate
Starch NF
Povidone USP
Talc USP
Colloidal Silicon Dioxide NF
Magnesium Stearate NF
Crospovidone NF

Hydroxypropyl Methylcellulose USP
Polyethylene Glycol NF
Titanium Dioxide USP
Ferric Oxide NF
Talc USP

IV. Review Overview

The sponsor has submitted 22 studies along with numerous pilot in-vitro studies. Out of these, 19 studies have been reviewed in full length and important conclusive observations from the other studies have been documented in this review. The organization of the studies is given in the Index on page 2, which will facilitate the reader to get an overview of the different studies submitted in support of the clinical pharmacology and biopharmaceutics of leflunomide. The conclusions and comments have been provided at the end of each section. The overall conclusions from the "Pharmacokinetics section" of the NDA are provided at the end of this review.

Following oral administration, leflunomide is rapidly converted to the active metabolite, A77 1726. Parent leflunomide is occasionally seen at very low levels. The outstanding characteristic of the pharmacokinetics of A77 1726 is its long half life (~15 days). Oral administration of activated charcoal or cholestyramine is effective in enhancing the elimination of A77 1726 in case of overdose or increased incidence of adverse events, decreasing the half-life to ~ 24 hours. The details of the pharmacokinetics of A77 1726 are discussed in the following sections.

METABOLISM-MECHANISTIC STUDIES

(A) In Vivo Studies

Animal studies have suggested that the metabolism of leflunomide takes place during passage through both the gut wall and the liver, although the site of first-pass metabooism has not been confirmed in man. A couple of in vivo metabolism mechanistic studies have been performed by the applicant to characterize the metabolic pathway in man and are discussed below.

Study # GB 101: ***Pharmacokinetics and metabolism of Leflunomide in healthy male volunteers following oral administration of ^{14}C-labelled compound.***

The pharmacokinetics and metabolism of Leflunomide after oral administration of ^{14}C-labeled drug (for position of label, see Appendix, page A3) has been examined in three healthy volunteers in this study. The study design is sketched on page A2 of the Appendix along with analytical validation data on page A3. The metabolic fate of approximately 35% of the dose (21.7% in urine and 14.4% in feces) was established within 72 hours post dosing of 100 mg leflunomide. The observations from this study are summarized below.

Plasma metabolites

A77 1726 was the single plasma metabolite observed.

- *Total radioactivity in plasma:*

The total radioactivity and plasma A77 1726 concentrations were superimposable and pharmacokinetic parameters were about the same (see Tables below).

Table :Pharmacokinetic parameters of total radioactivity in plasma following 100 mg ^{14}C-leflunomide containing 1.85 MBq radioactivity

Subject	C_{max} (µg.equiv/g)	T_{max} (hours)	AUC_{0-864} (µg.equiv.h/g)	$AUC_{0-\infty}$ (µg.equiv.h/g)	$T_{1/2}$ (days)
1	9.11	6	2432.5	2549.6	7.64
2	6.48	5	1642.4	1735.4	8.11
3	6.81	24	1861.5	1920.1	7.39
Mean	7.47	11.67	1978.8	2068.4	7.71
SD	1.43	10.69	407.9	426.9	0.37
% CV	19.2	91.7	20.6	20.6	4.7

- *A77 1726 in plasma*

Table : Pharmacokinetic parameters of A77 1726 in plasma following 100 mg ^{14}C-leflunomide containing 1.85 MBq radioactivity

Subject	C_{max} (µg.equiv/g)	T_{max} (hours)	AUC_{0-864} (µg.equiv.h/g)	$AUC_{0-\infty}$ (µg.equiv.h/g)	$T_{1/2}$ (days)
1	9.23	8	2589.2	2723.3	8.03
2	6.73	6	1722.9	1820.5	8.06
3	6.82	24	1958.4	2015.5	7.18
Mean	7.59	12.67	2090.1	2186.5	7.76
SD	1.42	8.87	448	475	0.50
% CV	18.7	77.9	21.4	21.7	6.4

- *Leflunomide in plasma, urine and feces:*

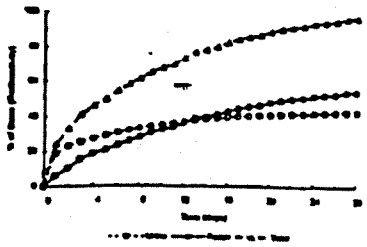
Leflunomide plasma concentrations measured up to 24 hours post-dose were below the quantitation limit (25 ng/ml), supporting extensive metabolism of leflunomide.

Reviewer's Comment:

In this study the LOQ is 25 ng/ml (assay Nov 1991) as compared to 5 ng/ml (assay Apr 1996) in the latter studies. The applicant has also not made any attempt to prevent the post sampling decomposition of leflunomide in samples by acidification of the collected plasma samples. A 30% loss of leflunomide in plasma samples was demonstrated in the assay validation at physiological pH. In the latter studies the sponsor has taken measures to prevent this loss by acidification of the collected plasma samples with hydrocholric acid (see assay validation on page A5 of the Appendix). In other studies, plasma levels of leflunomide have been observed (<25 ng/ml).

Urinary metabolites

- *Radioactivity in urine/feces:*



In the three subjects urinary excretion of radioactivity ranged from 30.8 to 58% of the dose and excretion of radioactivity in the feces ranged from 31.2 to 63.5% of the dose. The mean recovery (% of dose ± sd) in urine, feces and total was 42.8 ± 13.9, 48.2 ± 16.2 and 91 ± 2.9 respectively. The mean cumulative excretion of total radioactivity is shown the figure.

Fig: Mean cumulated excretion of total radioactivity

- *Identification of metabolites:*

U1 and U2 were two components detected in the urine. Deconjugation studies (incubation with β-glucoronidase) with U1 gave components U1A, U1B and U1C. Component U1A accounted for most of the radioactivity. Spectrum of U1A was consistent with X91 0228 (methyl-hydroxy A77 1726). Re-chromatography of U1A gave components U1A and U1C. Peak U1C was consistent with an isomer of X91 0228. It was postulated by the applicant that U1 was a glucoronide conjugate of methyl-hydroxy A77 1726 which after deconjugation isomerized from one isomeric form of X91 0228 to another. For easy visualization, the complete breakdown of various components detected in the urine has been shown schematically.

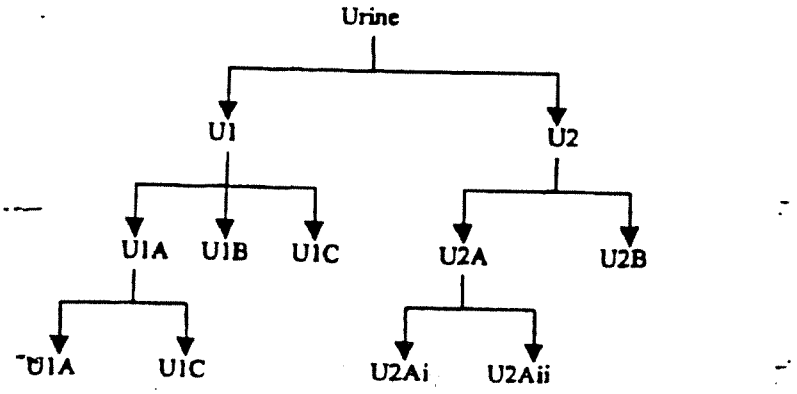


Figure: Schematic showing the components detected in the spectrum, where U1A, U1C, U2A, U2Ai and U2Aii were consistent with the spectrum of isomers of methyl-hydroxy A77 1726 and U2B was a peak consistent with TFMA-N-oxanilic acid.

Re-chromatography of U2 gave U2A and U2B. Deconjugation studies with U2A gave U2Ai and U2Aii. The spectrums of these two were consistent with that of X91 0228.

Therefore, it was postulated that U2A is also a glucoronide conjugate of methyl-hydroxy A77 1726, which after deconjugation to X91 0228, existed in two isomeric forms. Deconjugation studies with U2B gave component consistent with trifluoromethylaniline-N-oxanilic acid (TFMA-N-oxanilic acid). U3 was another component that was not identified.

In general in the urine samples TFMA-oxanilic metabolite (U2B) accounted for a mean of 9.7% of the dose. Hydroxylation of the methyl group and subsequent glucuronidation produced two isomeric forms (U1 and U2A) which accounted for a mean of 12% of the dose.

Percent of the dose excreted as these metabolites are tabulated below. After 72 hours there was insufficient radioactivity to allow further profiling.

Table : Percentage of dose corresponding to each urinary metabolite

Subject	Sampling time	% Dose Excreted	U1 (glucoronide conjugate of X91 0228)	U2A (glucoronide conjugate of X91 0228)	U2B (TFMA-N-oxanillic acid)	U3 (not identified)
1	0-24	18.10	8.31	3.31	5.30	1.19
	24-48	3.54	ND/NC	0.393	1.41	0.59
	48-72	1.63	ND/NC	ND/NC	1.30	0.326
	Total	**23.27**	**8.31**	**3.7**	**8.01**	**2.11**
2	0-24	21.30	8.75	4.24	7.09	1.21
	24-48	5.42	0.179	0.488	3.36	0.547
	48-72	4.20	ND/NC	0.508	3.69	ND/NC
	Total	**30.92**	**8.93**	**5.24**	**14.14**	**1.76**
3	0-24	15.9	5.44	3.05	3.75	1.40
	24-48	4.67	0.243	0.789	1.62	0.658
	48-72	1.77	ND/NC	0.273	1.50	ND/NC
	Total	**22.34**	**5.68**	**4.11**	**6.87**	**2.06**

ND/NC not detected/not calculated

Fecal metabolites

The mean recovery (% of dose ± SD) of the radioactivity in the feces was 48.2 ± 16.2, ranging from 31.2 to 63.5%. F1, F2 and F3 were three main fecal metabolites observed. Spectrum of F1 was consistent to A77 1726, F2 was consistent to methyl-hydroxy A77 1726 and F3 was identified as a reduced form of leflunomide. F1 accounted for 63-74% of the radioactivity in the 0-24 hour collection, corresponding to 4.7 to 6.3% of the total radioactive dose. F3 accounted for < 1% of the dose. The absence of parent leflunomide in the feces and the prolonged fecal excretion of radioactivity suggest extensive biliary elimination. The % of the dose excreted as these metabolites in the feces is given in the table below.

Table: Percentage of dose corresponding to each fecal metabolite

Subject	Sampling time	% Dose Excreted	F1 (A77 1726)	F2 (methyl-hydroxy A77 1726)	F3 (reduced leflunomide)
1	0-24	6.30	4.65	0.712	0.939
	24-48	1.74	1.32	0.155	0.266
	48-72				
	Total	**8.04**	**5.97**	**0.867**	**1.21**
2	0-24	-	-	-	-
	24-48	3.73	2.89	0.358	0.481
	48-72	6.65	5.43	0.412	0.805
	Total	**10.38**	**8.32**	**0.770**	**1.29**
3	0-24	10.00	6.28	0.760	1.88
	24-48	7.68	5.17	0.530	1.98
	48-72	4.06	4.06	ND	ND
	72-96	4.49	4.04	ND	ND
	Total	**26.23**	**19.55**	**1.29**	**3.86**

ND/NC not detected/not calculated

In brief, A77 1726 accounted for a mean of 11.3% of the dose and methyl-hydroxy A77 1726 accounted for a mean of 0.98% of the dose and reduced leflunomide accounted for a mean of 2.12% of the dose excreted in the feces.

Reviewer's Comments

- *Analytical validation for the detection of metabolites in the urine and feces has not been submitted.*
- *Validity of the determination of radioactivity in the biological samples has also not been submitted, although the methodology has been described.*

Conclusions

- A77 1726 is the major metabolite in plasma and feces. Urinary metabolites were methyl-hydroxy A77 1726 and TFMA-N-oxanillic acid. Other fecal metabolites were methyl-hydroxy A77 1726 and reduced leflunomide.
- Absence of parent drug in feces is consistent with extensive biliary elimination.
- Within the first three days of dosing the metabolic fate of only 35% of the dose (21.7% in urine and 14.4% in feces) could be established.
- At the end of 28 days the mean recovery (% of dose ± sd) in urine, feces and total was 42.8 ± 13.9, 48.2 ± 16.2 and 91 ± 2.9 respectiyely. From the results it could be speculated that renal route of elimination predominates during the first 24 hours, which is followed by a slower hepatic phase of elimination.

Study # 1022: *A study to determine the urinary metabolites of leflunomide using fluorine nuclear magnetic resonance.*

This was a non-radiolabeled study done in one normal healthy volunteer using a sensitive technique for analysis (Fluorine NMR), and was designed in order to allow profiling of the earlier metabolites of leflunomide by collecting urine in a series of smaller fractions instead of a single 0-24 hour collection in the radiolabeled study. This would reinvestigate whether leflunomide escapes first pass metabolism. 4 g cholestyramine was given three times daily after 96 hours of dosing with leflunomide to enhance the elimination of leflunomide (rationale discussed in the section 'Enhancement of Elimination' of this review). Post sampling decompostion of leflunomide to A77 1726 was prevented by adding 10µl of concentrated HCl to the plasma samples. Details of the study design are given on page A4 of the Appendix.

Urinary metabolites: Three main urinary metabolites were identified in this study- methyl-hydroxy-leflunomide glucoronide, methyl-hydroxy-A77 1726 glucoronide and TFMA-oxanilic acid. In study GB 101, both the glucoronides were thought to be of hydroxy-methyl-A77 1726. In study 1022, one of the glucoronides was identified to be from methyl-hydroxy-leflunomide. The figure shows that at 72 hours a total of 25% of the dose was recovered in urine, which is in agreement with the cumulative radioactivity (26%) measured in the urine from Study GB 101.

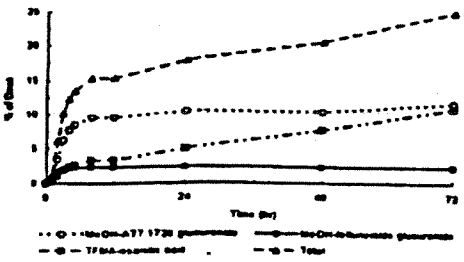
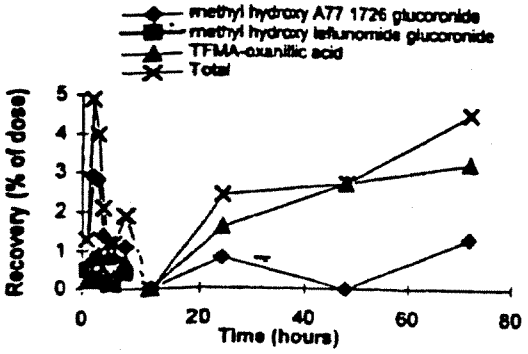
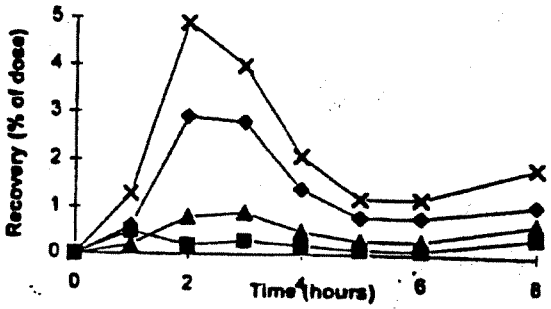


Fig: Cummulative urinary excretion of leflunomide Metabolites

The metabolic profile of these three metabolites till 72 hours post dosing and the first 8 hours post dosing is shown below. Based on the data, the excretion profiles for the metabolites submitted by the sponsor were not very accurate and has been re-plotted by the reviewer. The figure shows that the elimination of TFMA-oxanilic acid starts off slowly, but it continues for days after leflunomide dosing, whereas the glucoronides are eliminated within the first 8 hours of dosing. Methyl-hydroxy-A77 1726 glucoronide was also visible at 72 hours post dosing. By 72 hours after dosing, these metabolites accounted for 25% of the leflunomide dosed (TFMA-oxanilic acid accounted for 10.9%, methyl hydroxy A77 1726 glucoronide for 11.7% and methyl hydroxy leflunomide glucoronide for 2.4% of the leflunomide dosed). Peak hourly recoveries of the glucoronides were at two hours (2.9% of the dose) and for TFMA-oxanilic acid peak was at three hours (0.9% of the dose).



(a) Profile till 72 hours post dose



(b) Profile expanded for the first 8 hours

Figure: Excretion profiles of the major urinary metabolites following a single 100 mg oral dose

Sampling times (post-dose)	Plasma Conc A77 1726 (µg/ml)	Lef (ng/ml)
predose	ND	-
5min	-	ND
10 min	-	ND
20 min	-	ND
30 min	-	15.2
1 h	-	ND
2 h	-	ND
4 h	8.99	ND
8 h	-	ND
24 h	7.39	-
72 h	6.20	-
168 h	1.93	-
336 h	0.31	-

- = no sample taken
ND = not detected

Plasma metabolites

Plasma concentration of leflunomide and A77 1726 is shown in this Table. 0.31 µg/ml of A77 1726 was present at 336 hours post dose. The concentration at 4 hours was 8.99 µg/ml. The mean C_{max} observed in Study # GB101 was 7.59 µg/ml with T_{max} ranging from 6 to 24 hours.

Conclusions

- One of the glucoronides was thought to be coming from methyl-hydoxy leflunominde as opposed to from methy-hydroxy A77 1726 as suggested in the previous study (GB101).
- At 72 hours a total of 25% of the dose was recovered in the urine, which is in good agreement with the urinary recovery of 26% of the total radioactivity during the same time in study GB101.
- Complete credence cannot be obtained from a study of N=1, therefore, the results can only be informative and not conclusive.

Study # 1024: *Safety and pilot pharmacokinetics of i.v. A77 1726, and early investigation of urinary metabolite formation.*

This study was designed with the use of labeled A77 1726 with the non radioactive isotope, ^{13}C, to allow differentiation between the formation of TFMA-oxanilic acid from metabolism of TFMA and the side chain degradation of A77 1726, i.e. to clarify the pathway from A77 1726 to the major metabolite TFMA-oxanilic acid, and to establish

the origin of methyl-hydroxy-A77 1726 and its glucoronide conjugation. Each volunteer received a 10 mg intravenous infusion of A77 1726 over 2 hours. An infusion of 2 hours was selected to approximate the concentration time profile of A77 1726 observed after oral administration of the corresponding dose of leflunomide. On day 15 of the study (336 hours after the start of infusion), 4 g of cholestyramine was given t.i.d for 72 hours. Detailed study design is given on page A6 of the Appendix along with position of the label of page A7 and individual subject data on pages A8-A10.

Plasma metabolites

- *A77 1726 in plasma*

The concentration profile characteristics of A77 1726 after constant infusion of 10 mg A77 1726 for 2 hours is shown in the table below.

Characteristic	Mean ± s.d.
Cmax (mg/ml)	1.240 ± 0.158
tmax (h)	2.17 ± 0.41
AUC(0-23) (mg.h/l)	20.50 ± 1.50
AUC(0-48) (mg.h/l)	41.21 ± 3.37
AUC(0-96) (mg.h/l)	76.05 ± 8.15
AUC(0-336) (mg.h/l)	204.80 ± 28.88
AUCtotal (extrapolated beyond 336 h)(mg.h/l)	335.13 ± 75.85
% extrap.	37.8 ± 6.2

N=6

The model-independent and model-dependent pharmacokinetic characteristics are summarized in the table below.

Characteristic	Model-independent	Model-dependent (1-compartment)
	Mean ± s.d.	Mean ± s.d.
AUCtotal (mg.h/l)	335.13 ± 75.85	350.51 ± 96.21
% extrap.	37.8 ± 6.2	40.3 ± 8.4
CLtot (ml/min)	0.5213 ± 0.1289	0.5081 ± 0.1459
CLtot (ml/h)	31.28 ± 7.73	30.49 ± 8.76
CLtot (ml/h/kg BW)	0.3796 ± 0.0648	0.3691± 0.0781
MTvss (h)	350.8 ± 59.2	378.6 ± 89.4
Vss(l)	10.626 ± 1.058	10.931 ± 0.792
Vss(l/kg BW)	0.1301 ± 0.0087	0.1342 ± 0.0079
t1/2.1 (h)	242.8 ± 40.5	263.1 ± 62.0
t1/2.2 (h)	-	1.1114 ± 0.4782
Vc (l)	-	6.934 ± 1.012
Vc (l/kg BW)	-	0.0847 ± 0.0077

The concentration-time profiles for each subject showed a distribution phase with an average half-life of about 1h (t1/2.2 in the table above). This distribution phase has only occasionally been observed after oral administration of leflunomide.
After cholestyramine administration for three days after 336 hours of infusion of A77 1726, the plasma concentration of A77 1726 decreased below the LOQ (0.1 µg/ml) in all, but one of the subjects. This subject (2) also had the highest concentration of A77 1726 before the administration of cholestyramine.

- *TFMA in plasma*

No plasma level of TFMA was detected in the plasma (LOQ 1ng/ml), and was not possible to assess any potential influence of subject acetylator status on the N-acetylation of TFMA.

Urinary metabolites

Following administration of A77 1726 intravenously to healthy volunteers, a single metabolite, 4-trifluoromethyloxanilic acid (TFMA-oxanilic acid) was eliminated to a very small extent in the 0-24 hour urine, mostly below the LOQ (50 ng/ml). The hourly rate of oxanilic acid excretion was roughly constant for each volunteer over the 24 hours. The recovery of TFMA-oxanilic acid was lower than would have been predicted from oral leflunomide studies. It was postulated that it could be possible that there exists a supplementary pathway to oxanilic acid via methyl-hydroxy-A77 1726 glucoronide and A81 3226.

$^{13}C_2$-4-trifluoromethyloxanilic acid ($^{13}C_2$ TFMA-oxanilic acid) was quantified (10 out of 36 urine samples), but levels were low. $^{13}C_2$ TFMA-oxanilic acid increased from 0.0073 µg/ml in 0-2 hour urine to 0.0702 µg/ml in 8-24 hour urine. Total recovery in the first 24 hours after starting the infusion, expressed as a percentage of dose, ranged between 0.54 and 0.99 %. 98% of ^{13}C-label was retained in the metabolite, suggesting that TFMA is not a significant intermediate in the metabolic breakdown of A77 1726.

Specific assay for methyl-hydroxy-leflunomide glucoronide and methyl-hydroxy-A77

1726 glucorónide, measured as X91 0228 gave no values above the LOQ (50 ng/ml). This is in agreement with the postulation that following oral administration of leflunomide, the urinary methyl-hydroxy-leflunomide glucoronide and methyl-hydroxy-A77 1726 glucoronide are derived from the leflunomide by oxidation prior to isoxazole ring opening rather than direct metabolism of A77 1726. No other urinary metabolites were identified by the ^{19}F-NMR spectroscopy as well.

These results agree with findings in other studies in which circulating A77 1726 is cleared slowly from the body, the routes of elimination being biliary for intact compound and renal for oxanilic acid.

Figure: Proposed Metabolic pathway of leflunomide (HWA 486) in man

Conclusions

Reviewer's Comments

- *Analytical validation report for TFMA-oxanilic acid is not submitted, but SOP reference number is given. Assay validation report for methy-hyddroxy leflunomide and methyl-hydroxy A77 1726 glucoronides are also not submitted.*

- *The sponsor has proposed the above pathway of metabolism of leflunomide (HWA 486) in man. However, the metabolism mechanistic studies submitted as part of Clinical Pharmacology do not explain the pathway in fullness. This pathway was presented in one of the documents in the NDA and was cross-referenced to document number 16639. No detail information about the pathway was obtained from this document upon its request on the 90-day meeting. This pathway has been presented as part of the review, however, it should only be considered a proposed pathway. The percentages of the dose converted to the major metabolites have not really been tied down from any of the three metabolism mechanistic studies submitted.*

  The metabolism report is not very specific on terms of the site of metabolism either. However, most of the metabolism is suspected to be taking place in the liver.

(B) <u>In Vitro Studies</u>

Studies with human liver microsomes showed that isoxazole ring opening of leflunomide to A77 1726 was catalyzed by both catalytically active, and to a lesser extent, inactive microsomal protein. Soluble protein (cytosol) also catalyzed this ring opening. Subcellular fractions from human gastrointestinal tract were also able to catalyze this ring opening. Further metabolism of leflunomide (other than ring opening) in human liver samples in vitro was minimal. Metabolism was detectable from donor samples high in CYP3A4 activity. Further details of the role of isoenzymes of CYP 450 has been discussed on page 34 of this review.

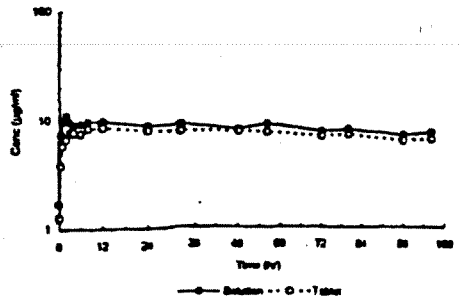
ABSORPTION

(A) Bioavailability (Relative BA)

The bioavailability of 100 mg leflunomide tablet relative to a solution (aqueous alcoholic PEG 400) was studied in the following study.

Study # D110:

Leflunomide has low aqueous solubility (21 mg/l at pH 4.8 and 6.8), hence the bioavailability of a tablet formulation has been compared to a standard aqueous alcoholic PEG 400 solution. The maximum plasma concentrations were lower with the tablet and reached at later time after administration of the tablet. This would be an expected difference between the two formulations. Based upon the treatment ratios for C_{max}, AUC_{0-104} and $AUC_{0-\infty}$, the bioavailability of the tablet relative to the solution was 80%.



Elimination half-life averaged 8 to 9 days and was essentially the same regardless of treatment. Although plasma concentrations were measured for approximately one-half of the half-life (104 hrs or 4.3 days), plasma concentrations after either formulation showed monoexponential decay from 12 hours through 104 hours with the same slope (see figure) and the AUC_{0-104} and $AUC_{0-\infty}$ ratios, tablet to solution, were the comparable (0.87 and 0.80, respectively). This suggests that collection of data through 104 hours provided a reasonable comparison of the tablet and solution. The mean ± SD of the pharmacokinetic parameters are tabulated below. For details see page A11-A12 of the Appendix.

Parameter	Solution	Tablet
C_{max} (µg/ml)	11.7 ± 1.5	9.5 ± 1.7
T_{max} (hr)	3.1 ± 4.4	5.7 ± 4.3
AUC_{0-104} (hr x µg/ml)	872 ± 152	761 ± 138
$AUC_{0-\infty}$ (hr x µg/ml)	3324 ± 1480	2661 ± 771
$t_{1/2}$ (days)	9.0 ± 3.0	8.4 ± 3.0

(B) Effect of food on bioavailability

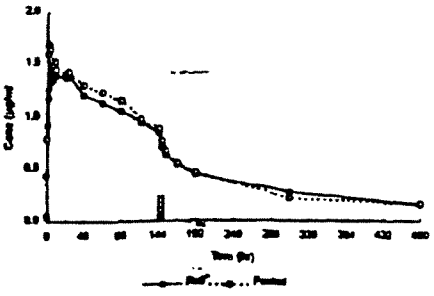
Study # GB 103:

The effect of food on the bioavailability of leflunomide from the 10 mg tablet was examined in 10 healthy volunteers receiving a single 20 mg (2x10 mg tablets) dose. Plasma samples were collected for 20 days (480 hours) after each treatment with a 7 week washout separating each phase. 50 g of charcoal was administered at 144, 147 and 150 hours after drug administration, to test the hypothesis that charcoal enhances the elimination of A77 1726. Details of the study design is given on page A13 of the Appendix. Since charcoal enhances elimination (discussed in section 'Enhancement of Elimination' of the review), it is more appropriate to use data only through 144 hours for pharmacokinetic analyses.

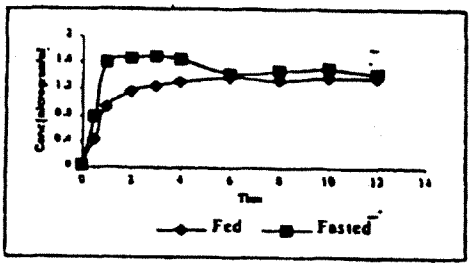
A standard breakfast was taken within 15 minutes prior to the administration of leflunomide. The standard breakfast under fed conditions consisted of two egg muffins with 100 ml orange juice with a nutritional value of :

fat	30 g
protein	41.8 g
carbohydrate	51.8 g
fibre	3.8 g
energy	640 Kcals

This diet is lower in fat content as compared to the recommended FDA high fat breakfast (30.8 g vs 55 g). The volume of fluid intake along with the food is also lower. The content of food as well as the volume of fluid intake would affect the drug absorption.



(a) For 480 hours



(b) The first 12 hours expanded

Figure: Mean plasma A77 1726 concentrations after administration of 20 mg of leflunomide under fed and fasted conditions to healthy volunteers (the vertical lines in figure (a) indicate the time of administration of activated charcoal)

The results of the study show that food had minimal effect on the plasma concentrations of A77 1726 with difference being observed for the first 6 hours of dosing reflecting the

T_{max}. The pharmacokinetic parameters under fed and fasted conditions are tabulated below. There was a decrease in the rate of appearance of A77 1726, as evidenced by an approximate 3-fold increase in T_{max} and a slight decrease in C_{max}. However, the 90% confidence intervals were within the 80%→ 125% window.

Parameter	Fed	Fasted	90% Equivalence Interval
C_{max} (µg/ml)	1.5 ± 0.3	1.8 ± 0.4	81→95%
t_{max} (h)	11.5 ± 11.2	3.5 ± 4.1	
AUC_{0-144} (µg.hr/ml)	163 ± 31.2	175 ± 53.4	83→105%
$AUC_{0-\infty}$ (µg.hr/ml)	422 ± 271	420 ± 193	80→115%
$t_{1/2}$ (days)	7.8 ± 3.9	7.4 ± 2.2	

The individual subject data and statistical analysis is attached in the Appendix on pages A14 to A16. Further the effect of oral charcoal administration on the $t_{1/2}$ of A77 1726 showed consistent results as that seen in a single volunteer study (GB102 on page 26) and the $t_{1/2}$ (hr) are tabulated below.

Study Period	Fed	Fasted
Before charcoal (24→144 h)	178	182
During charcoal (144→150 h)	20	15
After charcoal (168→480 h)	184	189

Conclusions

Based on the study design and diet, food does not seem to have an impact on the pharmacokinetics of leflunomide at the 20 mg dose.

Reviewer's Comment:

- *The food study was conducted on a 2x10 mg tablets, however, it is generally recommended to conduct the food study on the highest strength available (i.e. 100 mg is the highest strength available). The 20 mg dose did not show any food effect in terms of extent of absorption. Upon consultation with the medical reviewer, it was found out that the pivotal clinical trials (US 301 and MN 302) were done without any dietary restrictions. However, in study MN 301, specifications were given that the doses should be given with the meals. In all the PK studies with 100 mg leflunomide, the dose was administered after an overnight fast. The Medical Reviewer did not see any difference in the toxicity profile of the two studies with and without diet restrictions. Appropriate labeling comments with the consultation of the Medical Reviewer should be made.*
- *The high fat diet was also different as compared to the recommended FDA high fat diet, but given the long half-life of the drug the impact of the diet may not be significant.*

MULTIPLE DOSE PHARMACOKINETICS

(A) In healthy subjects:

Study # D111:

The objective of this study was to evaluate the degree of accumulation of A77 1726 in plasma and its tolerance in healthy subjects after administration of a single dose of 100 mg of leflunomide for 14 days. Details of study design are on page A17 of the Appendix.

A77 1726 in plasma

Plasma profiles of A77 1726 from the first dose of leflunomide in the multiple-dose regimen were fitted using the curve-fitting program and the parameters obtained are tabulated below. Plasma samples were collected only till 24 hours after the first dose. Determination of $T_{1/2}$ of A77 1726 from the first dose of leflunomide led to considerable underestimation, which led to poor multiple dose predictions. Better agreement was obtained between predicted and observed 14-day levels using data from a separate single dose study (#D110) in which sampling was extended beyond 24h to 104h. (compare $C_{ss(min)}$ values and $T_{1/2}$ from the two studies in the table below). Individual subject means are provided on pages A18-A19 of the Appendix.

Parameter ± SD	Study # D111	Study # D110
$T_{1/2}$ (h)	72.8 ± 27.6	183.6 ± 72.3
C_{max} (µg/ml)	12.11 ± 2.08	9.5 ± 1.7
T_{max} (h)	5.2 ± 4	5.7 ± 4.3
$C_{ss(min)}$ (predicted) (µg/ml)	46.1 ± 20.7	98.7 ± 45.3
$C_{ss(min)}$ (observed) (µg/ml)	83.4 ± 35.3	

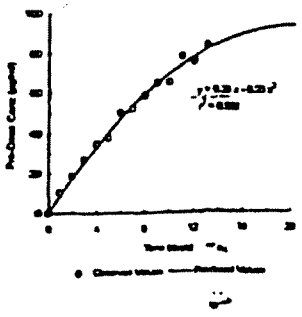


Fig: Mean pre-dose A77 1726 concentration after 100 mg/day leflunomide after 14 days

Steady state levels were not attained even after the 14th day of dosing. Because of the very long half life calculated for the single dose profiles, the predicted time to steady state plasma concentrations was much longer (> 20 days). As shown in the figure the steady state pre-dose concentration would be ~93 µg/ml. After 14 days of dosing the mean pre-dose concentration was 83 µg/ml which is about 90% of steady sate. The accumulation of A77 1726 was quite considerable during this time, giving serum levels approximately 10 times higher than those from a single dose. Meaningful estimates of A77 1726 half life after the last dose are difficult to obtain from this study, due to the relatively infrequent sampling after the dose. The very large standard deviation with the half-life (338.1 ± 210.4 h) reflects the poor confidence in the measurement. The C_{max} after 14 days of dosing was 92.1 ± 34.3 µg/ml as opposed to 12.11 ± 2.08 µg/ml after the first dose (8

fold increase). The long half-life of A77 1726 explains for this accumulation after multiple dosing. The ratio of area under the mean plasma concentration-time curve from 0-24 hours after last (2053 µg.h/ml) and first doses (242 µg.h/ml), 8.5 is another estimate of the accumulation ratio and is consistent with ratio of mean C_{max}s (7.8).

The concentrations of TFMA in plasma have been presented in the Appendix on page A20. The concentrations ranged from 1.5 to 7.1 ng/ml during 312-336 hours post initial dose. The sponsor has assessed the TFMA plasma concentration in the pharmacokinetic studies due to the concern of TFMA being mutagenic in animal studies. However, the C_{max} of TFMA was about 5000 times lower than that of A77 1726 levels.

A77 1726 in urine

The recovery of A77 1726 is shown on page A20 of the Appendix. The highest concentration of A77 1726 in urine was 0.4 µg/ml, although in most samples A77 1726 concentrations were below the limit of quantification (0.1 µg/ml). Full method development for the detection of A77 1726 was not done due to negligible amounts in the urine. Only between 272 and 934 µg (0.02 and 0.07% respectively, of the single 100 mg leflunomide administered for 14 days) was recovered in 6 out of 10 subjects treated with leflunomide.

Reviewer's Comment

- *In this study the applicant states that most urine samples for A77 1726 were below the limit of quantitation (0.1 µg/ml), but in the report for study D110 (Vol 1.68) also conducted at the same year (Mar 1982), the limit of detection for analysing samples in the urine was set to 20 ng/ml. As mentioned above full method development was not done.*

Loading and maintenance dose rationale for healthy subjects

The long $t_{½}$ and subsequent long time required to reach steady state indicates that a loading dose would be appropriate for leflunomide. Assuming that loading (D_L) and maintenance (D_M) doses are related through

$$D_L = \frac{D_M}{1 - e^{-\beta\tau}}$$

where β is the elimination rate constant and τ the dosing interval, a $t_{½}$ of ~ 7 → 8 days (Studies GB101 and D110) predicts that the loading dose should be ~ 10 → 12 fold higher than the maintenance dose. Consequently, a 100 mg loading dose would be suitable for a 10 mg maintenance dose.

Conclusions

- After 2 weeks of dosing of 100 mg leflunomide, the serum concentrations were 10 times higher than after a single dose of 100 mg.
- The ratios of the AUCs after the last and first dose is 8.5 and the ratio of the mean C_{max}s is 7.8 suggesting the high accumulation of A77 1726 on multiple dosing, which is consistent with the observed plasma half-life.

(B) <u>In Patients with Rheumatoid Arthritis</u>

Study # YU 204:

This study was designed to assess the pharmacokinetics and pharmacodynamics of leflunomide in patients with severe RA receiving daily doses of leflunomide for 6 months. 3 groups of RA patients (18 in each group) received daily doses of 5 mg/day (50 mg loading dose), 10 mg/day (100 mg loading dose) and 25 mg/day (100 mg loading dose). The loading dose was given on Day 0 and the maintenance dose on the next day. Plasma samples were collected over a 32-week period and analyzed for A77 1726 and TFMA. Details on page A21.

The mean ± SD and ranges of the pharmacokinetic parameters obtained for A77 1726 after administration of leflunomide for 24 weeks are summarized below. The mean data is attached in the Appendix on pages A22-A24. The 25 mg/day dosage regimen showed high inter-patient variability. A dose proportional increase in trough concentrations was seen in the 5 and 10 mg dosing regimen. Following 25 mg/day the mean trough concentrations were not truly dose proportional. There were two subjects (10 and 32) that were outliers with extremely high C_{24}(ss) concentrations. Due to this high inter-patient variability definite conclusions cannot be made. The variability in the $t_{1/2}$ values was also very high, especially in the 25 mg/day group, ranging from 6-40 days. Mean concentrations 24 hours after administration of a 50 mg loading dose were one-half of those observed after administration of 100 mg and the 2 groups receiving 100 mg loading doses (10 mg/day and 25 mg/day) had essentially the same values (see Table). Due to small subject number and high inter-patient variability, no conclusion regarding dose proportionality could not be obtained from this study.

TFMA was only detected in 9/18 samples of the 25 mg/day dosage regimen, with C_{max} ranging from 2-4 ng/ml and a t_{max} of 56-112 hours. No detectable TFMA were found at the end of the post-treatment observation period in all the groups.

	Maintenance (Loading) Dose		
Parameter	5 mg (50 mg)	10 mg (100 mg)	25 mg (100 mg)
C_{24} (Day 1) (µg/ml)	4.0 ± 0.6	8.4 ± 2.1	8.5 ± 2.2
C_{24} (SS) (µg/ml)	8.8 ± 2.9	18 ± 9.6	63 ± 36

Time to SS (weeks)	7.0 ± 1.4	6.8 ± 2.5	8.5 ± 4.3
$t_{1/2}$ (days)	15 ± 3	14 ± 5	18 ± 9

Age Trend Analysis

The covariance analysis using dose, age and BMI as independent variables performed to investigate if the concentrations of A77 1726 after 6 months of treatment are dependent on the age or BMI of patient, showed that the plasma concentrations were dose-dependent ($p < 0.001$), but neither age nor BMI had a significant influence. Two patients of age 60 years (8 and 32) had unusually high plasma concentrations, which lead to a small p-value for the variable "age". The $t_{1/2}$ analysis with respect to age and BMI is also tabulated below. No subjects less than 40 years were included in 25 mg/day regimen and there was high variation in this group as well, hence, difficult to draw conclusions regarding the effect of age on the $t_{1/2}$ of this group. The figures showing the effect of age on the plasma concentration and $t_{1/2}$ are attached in the Appendix on page A25.

Source (adjusted for all other variables in model)	DF	Sum of Squares	Mean Sum of squares	F-value	p-value
Css					
dose	3	36665.4	12221.8	21.13	0.0001
BMI	1	160.8	160.8	0.28	0.6006
age	1	2146.0	2146.0	3.71	0.0604
Model	5	102778.1	20555.6	35.55	0.0001
Error	45	26023.0	578.3		
T1/2					
dose	3	131.8	43.9	1.16	0.3339
BMI	1	12.1	12.1	0.32	0.5748
age	1	168.4	168.4	4.46	0.0403
Model	5	12634.8	2527.0	66.9	0.0001
Error	45	1698.8	37.8		

Loading and maintenance dose rationale in patients

Based upon a $t_{½}$ of ~ 15.7 days (see Table p20, averaged across doses), the loading dose in the target population should be 23 times the maintenance dose, or 230 mg for a 10 mg per day regimen. Since 100-200 mg per day was the highest single daily dose that had been studied in clinical trials, a loading regimen of 100 mg per day for 3 days was thought by the sponsor to be sufficient in most patients. Based on the calculation and the poor solubility of the drug, the three day loading regimen of 100 mg daily seems reasonable.

Further steady state pharmacokinetics of leflunomide from patients with RA was obtained from studies **US 201, YU 210/202 and YU 206.** In studies US 201 and YU 201/202,

patients received 5 mg/day (50 mg loading dose), 10 mg/day (100 mg loading dose), or 25 mg/day (100 mg loading dose) for 6 weeks. The plasma concentrations after the final dose $C_{6\,weeks}$ increased in a dose related manner. The $t_{1/2}$ averaged between 10-19 days with a range of 9 to 30 days across patients. The mean ± SD pharmacokinetic parameters from these studies are summarized below:

Maintenance (Loading) Dose			
Parameter	5 mg (50 mg)	10 mg (100 mg)	25 mg (100 mg)
C_{max} (µg/ml)	8.3 ± 4.2	24.4 ± 28.8	57.2 ± 29.6
$C_{6\,weeks}$ (µg/ml)	6.3 ± 3.4	17.4 ± 9.7	29.5 ± 13.7
$t_{1/2}$ (days)	12 ± 3	16 ± 7	13 ± 4

C_{max} values are from study US 201 and $C_{6\,weeks}$ $t_{1/2}$ from study YU 201/202

Age Trend analysis

No correlation was seen age, BMI and serum levels of A77 1726, although a week positive correlation was found between age and half-life from study YU 201/202.

Study # YU 205:

This study was an open-label extension study for patients in studies YU 204 and YU 203 to obtain more information on long term treatment (18-month) in RA patients. In the 6 month studies YU 203 and YU 204, patients were randomized to one of three daily leflunomide dosages: 5 mg with 50 mg loading dose, 10 mg with 100 mg loading dose or 25 mg with 100 mg loading dose. Study YU 203 also contained a fourth arm in which patients were randomized to placebo. Patients from study 203 entered study 205 directly without interrupting study medication and did not receive a loading dose. Patients from study 204, however, interrupted their study medication for 8 weeks before entering study 205. Therefore, they were given a single loading dose of 100 mg leflunomide at the start of the study. Patients from both studies received a daily maintenance dose of 10 mg for the first 4 weeks. The dose was then increased or decreased by 5 mg (range from 5 mg to 25 mg) every 4 weeks depending upon the efficacy or toxicity. Trough concentrations of A77 1726 were measured every 3 months and prior to a dosage change. The study description is on page A26.

Mean trough concentrations at 10 mg per day (19 µg/ml) and 25 mg per day (54 µg/ml) were in agreement with those measured in study YU 204 (18 and 63 µg/ml, for 10 and 25 mg/day, respectively). The number of measurements made at 5, 10, 15, 20 and 25 mg/day regimens were 14, 310, 251, 188 and 94 respectively. A log-log plot of A77 1726 concentration vs. dose between 10 mg and 25 mg/day was linear with a slope of 1.09 (r^2=0.995) (see section dose proportionality), supporting the linearity of A77 1726 kinetics. However, a discrepancy was seen at the 5 mg/day regimen. Due to the small

number of observations (N=14), definitive conclusions would be difficult to draw with this data.

Age and Gender Trend Analysis

After normalizing to a 20 mg dose, mean trough plasma A77 1726 concentrations were higher in women than in men. The difference between the means was 10 mg/l (women 30.5 mg/l, men 20.3 mg/l). Although, men and women had similar body mass index ranging from 17.1-32.7 kg/m^2 for men and from 15.7-43.7 kg/m^2 for women. A clear relationship between age and plasma concentrations of A77 1726 was also observed where elderly patients had higher plasma concentrations than younger patients. This trend could be well observed with the female patients (increase in plasma concentration with increase in age). However, similar analysis was not possible in male subjects due to smaller number of male subjects. This trend has been pictured in the graph. The 5 mg dosage group has been excluded from the analysis.

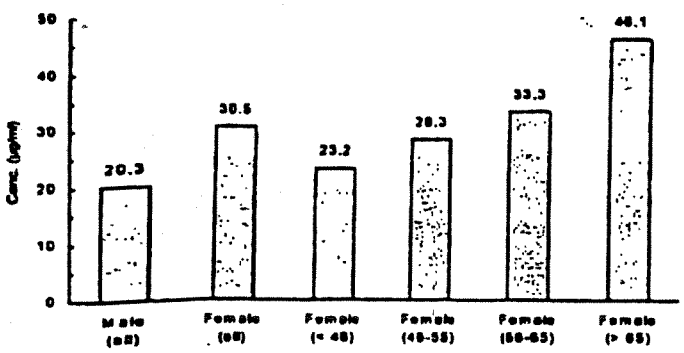


Figure: Mean A77 1726 trough plasma concentrations in male and female patients with RA after administration of 10 to 25 mg/day

Reviewer's Comment

Study YU 203 has been submitted as part of the Clinical section of this NDA. This study is similar to YU 204, but also has a placebo arm to it. In the Clinical Summary of the application the applicant has mentioned the choice of the 20 mg maintenance regimen was based on the efficacy and safety concerns from this Phase II study. Improved efficacy was observed with 25 mg dose as compared to the 10 mg, but was also associated with more adverse events. Therefore, a daily dose of between 10 and 25 mg was regarded as the optimal dose for majority RA patients.

Study # YU 206:

This multiple dose pulsing study was designed to assess the safety, tolerability and kinetic profile of leflunomide under pulsed administration up to 200 mg/week for 6 months and to determine whether deterioration in the patient's condition may occur at the end of a pulse interval. Patients were randomized to take weekly either 2 tablets of 100

mg leflunomide or 1 tablet of 100 mg leflunomide and a visually identical placebo. Both groups received a loading dose of 2x100 mg leflunomide, administered for two days (100 mg each). Details of the study design are outlined on page A27 of the Appendix.

The means ± SD for the $C_{ss(max)}/t_{ss(max)}$ and $C_{ss(min)}/t_{ss(min)}$ values for the 100 mg and 200 mg dosage regimen is tabulated below. The individual subject parameters are attached in the Appendix on page A28 along with the plasma concentration profiles and trough profiles on page A29.

Parameter	100 mg leflunomide per week (n=20)	200 mg leflunomide per week (n=21)
$C_{ss(max)}$ (µg/ml)	45.8 ± 15.2	85.9 ± 37.1
$C_{ss(min)}$ (µg/ml)	29.7 ± 15.4	59.3 ± 37.3
$t_{ss(max)}$ (hours)	98.2 ± 49.9	117.0 ± 51.9
$t_{ss(min)}$ (hours)	158.2 ± 27.7	164.0 ± 13.4

The results show that C_{max} and C_{min} increase in proportion to the administered dose. The mean steady state comparisons of C_{min} for study YU 206 and YU 204 is shown below. YU 204 was also a multiple dose study where patients were given daily doses of 10mg/day (weekly 70 mg) and 25mg/day (weekly 175 mg).

Study YU 206 (treatment phase- 6 mo)	Study YU 204 (treatment phase- 6 mo)
100 leflunomide per week 29.7 ± 15.4 µg/ml	10 mg leflunomide/day (70 mg per week) 17.98 ±9.6 µg/ml
200 leflunomide per week 59.3 ± 37.3 µg/ml	25 mg leflunomide/day (175 mg per week) 63.0 ± 36.2 µg/ml

TFMA plasma levels were below the detection limit in most cases (2 ng/ml). The maximum plasma concentration of TFMA was 3 ng/ml.

Conclusions

- The half live of A77 1726 in patients is ~ 15 days.

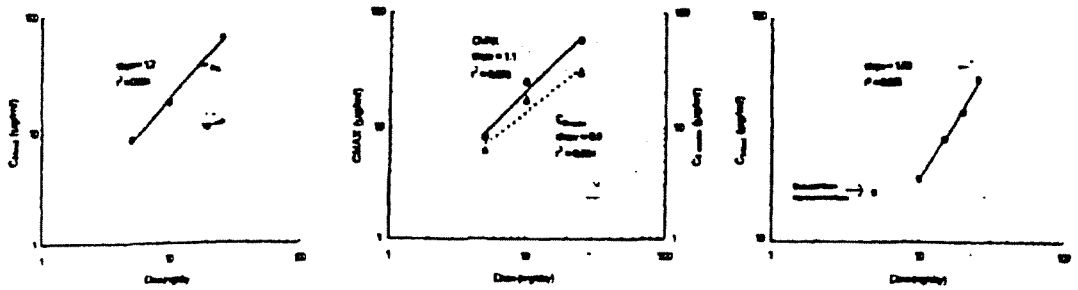
- Plasma concentrations are higher in women and increase with age as seen in study YU 205.
- It takes about 7-8 weeks to reach steady state with a single loading dose of 100 mg followed by a maintenance dose daily.

Reviewer's Comment

- *The maximum exposure at the maximum recommended dose (20 mg) at steady state (Study YU 204) has not been reported. The Pharmacology Reviewer would need this information for toxicity comparison with the animal data. The reviewer has calculated the rough estimation of the maximum exposure with the 25 mg tablet from study YU 204 based on the steady state trough values after the last dose to be 1512 µg.h/ml. This would however be an underestimation of the maximum exposure. The actual exposure can be calculated by taking into account the 0-12 h samples collected after the last dose at the end of 24 weeks.*
- *The 100mg D_L/20mg D_M dosage regimen has not been studied in the multiple dose PK study YU 204. However, the 10 and 20 mg tablets are dose proportional, have linear pharmacokinetics and clinical studies have been conducted in the same regimen.*
- *It was not very clear from the study design of YU 204 that trough levels of A77 1726 were measured for 24 weeks, however, the results report trough concentrations on Day 1 and at steady state.*

DOSE PROPORTIONALITY

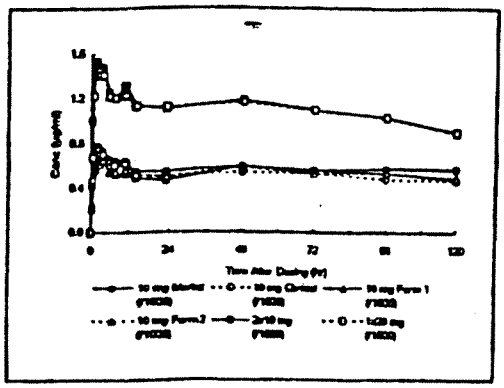
No formal dose proportionality study was conducted. Data from studies YU 204, YU 201/201, US 201 and YU 205 supported the linear pharmacokinetics of A77 1726. A log-log plot of steady state trough or C_{max} values vs. dose was linear in all these studies with a slope close to unity, indicating linear pharmacokinetics. However, high variability was also seen in some of these studies. Relationship between A77 1726 concentration at steady state and leflunomide dose after the administration of 5, 10 and 25 mg/day for different durations has been shown in the following graphs, suggesting linear pharmacokinetics of the drug in this range.



Duration: 24 weeks (YU 204) Duration: 6 weeks (YU 201/202, US 201) Duration: up to 18 mo (YU 205)

Reviewer's Comment

The variability gets shrunk in a log-log plot. In study YU 204 the 25 mg dose was not truly dose proportional, however, there was so much variability amongst subjects that no definite conclusions could be drawn.



Additional information regarding dose proportionality was obtained from bioavailability/bioequivalence studies 1036, 1030, and 1035, 10 mg and 20 mg doses of leflunomide have been administered to healthy volunteers according to identical protocols. Details of these studies will be discussed in the section 'Bioequivalence' in the latter part of the review. Plasma concentrations after administration of 2 x 10 mg or 1 x 20 mg are essentially twice those after administration of 10 mg doses and C_{MAX} and AUC_{0-120} increase linearly with dose (see Figures on the side and below). Taken as a whole, the data in patients with rheumatoid arthritis and in healthy volunteers provide sufficient evidence that the pharmacokinetics of A77 1726 are linear over the range of doses to be used clinically and that the 10 mg and 20 mg strengths are dose and dosage form proportional.

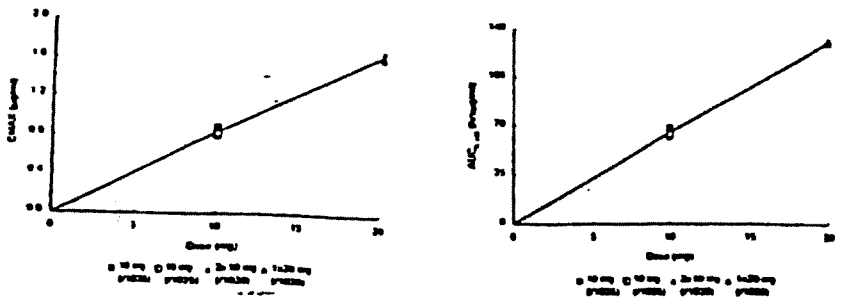


Figure: Relationship between Cmax and AUC after administration of 10 mg and 20 doses in the bioequivalence studies (1030, 1035 and 1036)

ENHANCEMENT OF ELIMINATION

Due to the extremely long half-live of A77 1726 it would be imperative to gain insight on methods to eliminate the drug faster from the system, especially in case of overdose and increased incidence of side effects. In this attempt, activated charcoal and cholestyramine were investigated as adsorbents that would bind to the drug in the gut and interfere with entero-hepatic recycling.